Active and Passive Smoking and Pathological Indicators of Lung Cancer Risk in an Autopsy Study

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Objective.—The association between involuntary smoking and lung cancer has been supported by most epidemiologic studies, but a number of authors and interest groups claim that the possibility of bias has not been excluded. Few autopsy-based studies have explored the role of active smoking and other exposures in lung carcinogenesis, and none has been previously done to examine the role of passive smoking. We have undertaken such an autopsy-based study in Athens, Greece.

Design.—Lung specimens were taken at autopsy from 400 persons 35 years of age or older, of both genders, who had died within 4 hours from a cause other than respiratory or cancer in Athens or the surrounding area. For each person at least seven tissue blocks were taken from the main and lobar bronchi and at least five blocks from the parenchyma, including an average of about 20 smaller cartilaginous bronchi and membranous bronchioles. The specimens were examined without knowledge of the exposures of the particular subject in Turin, Italy. For 283 (71%) of the subjects the preservation of the bronchial epithelium was satisfactory for pathological examination, and for 206 among them (73%) an interview could be arranged with their next of kin, focusing on smoking habits of the deceased and their spouses, as well as other variables. The interviewers were not aware of the results of the pathological examinations.

Main Outcome Measure.—Specimens were examined for basal cell hyperplasia, squamous cell metaplasia, cell atypia, and (in membranous bronchioles and bronchiolo-alveolar airways) mucous cell metaplasia, ie, pathological entities that may be lung cancer risk indicators or epithelial, possibly precancerous, lesions (EPPL). The gland and wall thicknesses were also measured and their ratio calculated (Reid Index).

Results.—In comparison with nonsmokers, EPPL values were significantly higher among current smokers and higher, but not significantly so, among former smokers. Furthermore, EPPL values were significantly higher among deceased nonsmoking women married to smokers rather than to nonsmokers. In this set of data neither occupation nor residence was associated with EPPL, but this could be due to the poor correlation of residential history with exposure to air pollution and the lack of adequate standardization of contemporary Greek occupations. The Reid Index was higher among smokers and former smokers in comparison with nonsmokers, among subjects with mainly urban residence in comparison with those with mainly rural residence, and among nonsmoking women married to smokers in comparison with those married to nonsmokers, but none of these differences was statistically significant.

Conclusion.—These results provide support to the body of evidence linking passive smoking to lung cancer, even though they are based on a study methodologically different from those that have previously examined this association.

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THE ASSOCIATION between exposure to environmental tobacco smoke and lung cancer, first reported in 1981,[1,2] has been supported by the collective evidence of several epidemiologic studies.[3-11] However, some authors[12,13] and a number of special interest groups[14] have challenged the epidemiologic findings, invoking the operation of unlikely but conceivable biases. To further examine the etiologic importance of involuntary smoking in lung carcinogenesis, we have undertaken an autopsy-based epidemiologic study in Athens, Greece. Lung specimens were examined without knowledge of the exposures of the particular subject for pathological entities that are considered lung cancer risk indicators, and the findings were correlated with independently elicited exposure information concerning the deceased and provided by his or her next of kin.[15] Several of the pathology-based studies[16-31] have examined the importance of tobacco smoking and various correlates of air pollution as risk factors of pathoanatomic indicators of lung cancer, chronic bronchitis, or respiratory performance, but there have been no previous such investigations of the role of involuntary smoking.

METHODS

Autopsies are mandatory in Greece when a death is due to external causes or has occurred within 24 hours after the development of symptoms and the patient has not been under the regular attendance of a physician who is willing to sign the death certificate. During a 4-year period (September 1986 through October 1990) about 12 000 autopsies were performed in the Coroner's Center of Athens, the major of two centers that cover the 4 million–large population of Attica. During this period one of us (E.A.), a pathologist specifically trained in the Turin center and collaborating with the Coroner's Center of Athens, obtained lung specimens from 400 persons 35 years of age or older, of both genders, who had

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Table 1.—Distribution of the Initially Selected 400 Subjects (A), the 283 Subjects for Whom Suitable Samples Were Taken (B), and the 206 Persons for Whom Both Suitable Samples and Interviews Were Available (C), by Cause of Death, Age, and Gender.

	Group		
	A No. (%)	B No. (%)	C No. (%)
Cause of death			
Coronary heart disease	234 (59)	170 (60)	139 (68)
Other cardiovascular diseases	42 (10)	32 (12)	20 (10)
Diseases of the digestive system	25 (6)	17 (6)	10 (5)
Diseases of the genitourinary system	4 (1)	4 (1)	3 (1)
Accidents and other external causes	58 (15)	46 (16)	34 (16)
Unknown (but nonrespiratory)	37 (9)	14 (5)	...
Age, y			
≤39	4 (1)	4 (1)	4 (2)
40-49	35 (9)	25 (9)	18 (9)
50-59	74 (19)	56 (20)	39 (19)
60-69	89 (22)	66 (23)	51 (25)
70+	173 (43)	121 (43)	94 (45)
Unknown	25 (6)	11 (4)	...
Gender			
M	275 (69)	203 (72)	144 (70)
F	117 (29)	80 (28)	62 (30)
Unknown	8 (2)	...	...

died within the last 4 hours from a cause other than respiratory or cancer. Specimens were collected when the indicated pathologist was on duty during the early morning hours at the Coroner's Center of Athens, and the 400 specimens were all that were available to him during his service at the time period of the study. The subjects were of Greek nationality and all died in the Attica area (which includes Greater Athens) but could have been current or past residents of any area of Greece. The pathological examinations were undertaken in Turin by two pathologists (F.M., L.D.) who were blinded about the identity of the subject and his or her past exposures.

For each subject, at least seven tissue blocks were taken from the main and lobar bronchi and at least five blocks from the parenchyma (one for each lobe), including an average of about 20 smaller cartilaginous bronchi and membranous bronchioles; additional blocks were obtained from scars and areas of fibrosis, when present. At least two histological sections were examined from each block.

In 283 (71%) of the subjects the preservation of the bronchial epithelium was satisfactory according to the criteria set by Auerbach et al,[17] and only these cases were considered suitable for further study. In these subjects several morphological features were examined to assess the precancerous potential in the bronchial tree.[16,17,20,21,24]

Basal cell hyperplasia, squamous cell metaplasia, and cell atypia were considered as lung cancer risk indicators or epithelial, possibly precancerous, lesions (EPPL) in main plus lobar and in other cartilaginous bronchi, whereas in membranous bronchioles and bronchiolo-alveolar airways, mucous cell metaplasia was also taken into account (14 variables). For each of these 14 variables several observations were available for every study subject. When absent EPPLs were graded as 0, or as 1 to 3 (1 to 4 for atypia) when present. The criteria for the scoring were based on the degree of changes for hyperplasia and atypia, and on the extension of changes around the airway circumference for squamous and mucous metaplasia. A set of photographic reference standards was prepared and used for comparison during examination and grading. Each slide was examined by the two pathologists and discussed when the grade scores were not in agreement.

The sum of the grade scores assessed for each of the 14 EPPL variables was calculated and expressed as a percentage of the maximum sum that could be obtained. Thus, for basal cell hyperplasia in main plus lobar bronchi, there were usually seven observations for every study subject (two for the main and five for the lobar bronchi). Each observation was assigned a grade from 0 to 3 (basal cell hyperplasia from absent to maximum), with a grade sum ranging from 0 to 21. If the actual grade sum were 7, its percentage expression of the maximum grade sum would be 33. The resulting percentage values of the 14 variables were then added. This method, introduced by Wright et al[22] in a morphological grading of bronchiolar lesions, allows the estimation of a total EPPL grade score. As Wright et al[22] have pointed out, this procedure usually generates a variant of the mean of all the grades, although in this instance, the method assigns equal weights to atypia (original scale from 0 to 4) and to hyperplasia or metaplasia (original scales from 0 to 3). The total EPPL grade score has a positively skewed distribution; most values lie between 10 and 80, with occasional values above 100.

Independently, the Reid Index (RI) was also determined for every study subject.[18] This index reflects bronchial mucous gland enlargement and has been regarded by several workers[20,23] as a morphologic counterpart of chronic bronchitis. The RI is calculated[18] as the ratio of the thickness of the bronchial mucous glands (G) to the bronchial wall (W) thickness (inner perichondrium to basement membrane), and is usually graded as 1 ($G/W \leq 0.35$), 2 ($0.35 < G/W \leq 0.50$), or 3 ($G/W > 0.50$). The index was evaluated in the two main bronchi and five lobar bronchi of each subject, and the mean value for this subject was then estimated.

An effort was made to identify the next of kin of the deceased. The interviewers, both medical doctors (X.Z., A.K.), explained by telephone or, more frequently, through an assistant the purpose of the study, and requested permission to visit and administer an interview in person. The interviewers were not aware of the results of the pathological examinations, which were performed without knowledge of the exposures of the particular subject. For 206 subjects an interview was done, whereas for the remaining 77 (27%) there was either refusal (48 persons) or loss of contact (29 persons). The interviewed persons were spouses (43%), children (19%), brothers or sisters (6%), other relatives (6%), or others (26%).

Table 1 shows distributions by diagnosis, age, and gender of the initially selected 400 subjects, the 283 persons for whom suitable samples were taken, and the 206 persons for whom both suitable samples and interviews were available.

The interviews were done with standardized questionnaires. Data concerning demographic characteristics were obtained, and information concerning occupation, residential history, and smoking habits of the deceased and his or her spouse was recorded. Specifically, the next of kin was asked to indicate, among other things, the employment history of the deceased; whether he or she was a smoker or an ex-smoker at the time of death and, if so, what was the average number of cigarettes per day; and where he or she has lived and for how long. For every married subject, smoking information about the spouse was also recorded.

Standard regression procedures were used for the analysis. The values for EPPL and RI were alternatively used as dependent variables. Independent variables were, in addition to gender, age and years of schooling of the deceased, resi-

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Table 2.—Cross-Classification of 206 Subjects by Reid Index (RI) and Total Score of Epithelial, Possibly Precancerous, Lesions (EPPL) in the Bronchial Tree

	EPPL					
RI	0-19	20-39	40-59	60-79	80+	Total
0.0-1.4	12	3	1	2	3	21
1.5-1.9	9	5	4	1	1	20
2.0-2.4	20	11	15	11	9	66
2.5-2.9	8	19	19	13	14	73
3.0	3	5	5	3	10	26
Total	52	43	44	30	37	206

Table 3.—Univariate Characteristics of the 206 Studied Subjects and Mean Values of Epithelial, Possibly Precancerous, Lesions (EPPL), by Group

Variable	No.* (%)	EPPL (SE)
Age, y		
35-49	22 (11)	67.45 (11.69)
50-59	39 (19)	56.74 (7.56)
60-69	51 (25)	48.86 (5.80)
70-79	63 (30)	38.92 (3.99)
80-89	28 (14)	48.36 (7.48)
90+	3 (1)	42.33 (27.51)
Gender		
M	144 (70)	47.82 (3.30)
F	62 (30)	52.19 (5.95)
Schooling, y		
0	15 (8)	46.40 (10.65)
1-6	96 (47)	51.22 (4.58)
7+	92 (45)	47.17 (5.78)
Occupational activity		
Professionals	5 (2)	70.40 (21.72)
Commercial, etc	20 (10)	40.15 (5.96)
Employees	53 (27)	42.53 (3.79)
Manual workers	72 (36)	55.18 (6.23)
Agricultural	14 (7)	54.00 (13.15)
Housekeeping	36 (18)	41.22 (5.84)
Residential history		
Mainly urban	152 (77)	49.88 (3.44)
Mainly rural	45 (23)	49.42 (6.37)
Smoking habits		
Nonsmokers	62 (31)	41.26 (5.61)
Ex-smokers		
1-20 cigarettes/d	19 (10)	45.37 (11.10)
21-40 cigarettes/d	9 (5)	31.78 (6.82)
41+ cigarettes/d	8 (4)	42.88 (9.09)
Current smokers		
1-20 cigarettes/d	51 (26)	58.92 (5.74)
21-40 cigarettes/d	37 (19)	61.43 (7.53)
41+ cigarettes/d	14 (7)	42.93 (6.54)

*There are missing values: years of schooling, three; occupational activity, six; residential history, nine; smoking habits, six.

dential history, and smoking habits. Specifically, the subjects were classified into those who lived most of their lives in urban areas (population of ≥100 000) and those who lived most of their lives in rural areas. With respect to smoking habits, current smoking and past smoking were introduced into the model as indicator variables, whereas the effect, if any, of the daily amount of cigarettes, among smokers and past smokers separately, was assessed by entering the appropriate terms in the model to restrict information to the relevant groups. Occupation of the deceased was also evaluated in the initial models using five indicator variables for professionals, urban blue-collar workers, agricultural workers, self-employed plus commercial workers, employees, and housekeepers.

RESULTS

Table 2 shows the cross-classification of the 206 subjects by EPPL and RI values. There is a fair degree of correlation (the correlation coefficient, based on individual pairs of observations, is +0.40), which is statistically significant ($P<.001$). Table 3 presents univariate distributions of these subjects by age, gender, years of schooling, most recent occupation, residential history, and smoking habits. This table also shows mean values and corresponding standard errors of EPPL by group. Due to intercorrelations among the various independent variables, the EPPL data in Table 3 are not directly interpretable.

Table 4 shows the results of multiple regression analysis using EPPL as a dependent variable and age, gender, smoking habits, and residential history as independent variables. Entering years of schooling and/or occupational groups into the model did not noticeably affect the regression coefficients, nor was there a substantial, significant, or suggestive association of EPPL with any of the occupational groups or with years of schooling. The values for EPPL were substantially and significantly higher among current smokers and higher, but not significantly so, among past smokers. There were no dose-response trends among current or past smokers. With the tobacco smoking terms in the model, EPPL values were significantly higher among female subjects, and there was a nonsignificant decrease with age. Residential history, which is a very crude indicator of long-term exposure to air pollution, was not associated with EPPL. Carcinoma was found in four elderly men (68 to 82 years) who were all heavy smokers (30 to 45 cigarettes per day). Their individual EPPL values were 29, 53, 142, and 253, with the mean equal to 119.

Among the 62 female subjects there were 41 nonsmokers. Among them 17 were married to husbands who were ever smokers, whereas 13 were married to never smokers (for 11 relevant information was not available). Nonsmoking women exposed to environmental tobacco smoke through their husbands had a significantly higher mean value of EPPL, although the estimates were not very precise. Thus, the difference (with the 95% confidence interval [CI]) was 27.88 (5.64 to 50.13), with a two-tailed P of .02. Adjustment for one or more of the other variables indicated in Tables 3 and 4 had no effect.

With respect to RI, no difference or association in the multiple regression analysis was significant at a nominal level ($P<.05$), although the results were, in general, in "expected" directions. Thus, compared with nonsmokers, RI was higher among smokers (difference, 0.125; CI, −0.090 to 0.340) and, to a lesser extent, among past smokers (difference, 0.050; CI, −0.210 to 0.310). The index was also higher among those with mainly urban residence (difference, 0.177; CI, −0.030 to 0.384) and among nonsmoking women married to smokers rather than to nonsmokers (difference, 0.220; CI, −0.149 to 0.589).

COMMENT

Studies linking pathoanatomic findings in the lungs with data concerning exposures to tobacco smoking and air pollution have concentrated on lesions thought to be risk indicators of lung cancer,[16,17,22,23,24] on pathological abnormalities associated with functional respiratory changes,[22,23,25] or on pathological changes linked to the clinical syndrome of chronic bronchitis.[18,22,25,28,29] The index proposed by Reid[18] as a morphologic correlate of bronchial mucus hypersecretion and, accordingly, chronic bronchitis[18,23] has been associated in some studies with tobacco smoking,[22,28,29] but there are no reports linking RI with air pollution or a proxy variable like residential history. In the present study no significant association was evident between the RI, on the one hand, and any of the exposure variables on the other, although the results were, overall, in expected directions, the index being higher among smokers and urban residents. This may imply that RI, as measured, is not a sufficiently sensitive indicator of the pathological changes associated with chronic bronchitis, or that the unavoidable nondifferential misclassification in exposure ascertainment led to attenuation of weak true associations. Nevertheless, the moderately strong and highly statistically significant association between RI and EPPL suggests that there are common factors in their etiology (although not necessarily with equally strong etiologic relations), and that the reliability of these measurements is not much lower than that of many other variables used in epidemiologic studies (for which the correlation coefficients vs their own standards are frequently between 0.5 and 0.6).

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Table 4.—Multiple Regression-Derived Regression Coefficients of Epithelial Possibly Precancerous Lesions on a Number of Independent Variables: Point Estimates, 95% Confidence Intervals, and Two-Tailed *P* Values*

Variable	Category	Regression Coefficient (95% CI)	Unit of Independent Variable	*P* (Two-Tailed)
Age	Continuous	−4.65 (−9.85 to 0.54)	10 y	.06
Gender	Male	Baseline		
	Female	17.10 (1.77 to 32.43)	NA	.03
Smoking habits	Nonsmokers	Baseline		
	Current smokers	23.52 (7.57 to 39.47)	NA	.04
	No. of cigarettes	−2.69 (−8.04 to 2.66)	10 cigarettes	.32
	Ex-smokers	7.39 (−11.95 to 26.73)	NA	.45
	No. of cigarettes	−0.32 (−7.73 to 7.09)	10 cigarettes	.93
Residential history	Mainly rural	Baseline		
	Mainly urban	−4.89 (−20.25 to 10.47)	NA	.53

*CI indicates confidence interval; and NA, not available.

approach of the present study drew heavily from the studies done by Auerbach and colleagues[18,17,20,21,24] over a period of 30 years. These pioneering studies are of great relevance in evaluating pathological lesions, although it is possible that minor biases may have been introduced in their sampling procedures; furthermore, there has not been a complete consensus on the relative value of the early lesions as predictors of the future occurrence of tumors.[24] We have also used the semiquantitative scoring system that was introduced by Wright and her colleagues,[22] a system that imparts an element of objectivity to the summarization of the pathological findings.

Auerbach and colleagues[16] postulated that there should be changes in the bronchial epithelium of patients with lung cancer, as well as in smokers, that differ markedly from those in nonsmokers. They have focused on four types of epithelial changes (basal cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ) and found that these changes (mainly cells with atypical nuclei) were much more common in smokers (particularly heavy smokers), whereas among past smokers the findings were minimal and, among nonsmokers, urban residence had little and age and gender virtually no effect (if anything, older women had fewer changes).[17,20,21] In a later study, Auerbach et al[24] have shown that smoking of low tar and nicotine cigarettes generates substantially fewer histological changes in the bronchial epithelium. The results of the Auerbach studies do not necessarily imply that all the indicated epithelial lesions represent stages of a unidirectional carcinogenic process; indeed, the findings of other studies[3,25] suggest that some of the detectable epithelial lesions are likely to be correlates rather than intermediate steps in lung carcinogenesis.

With respect to demographic variables (broad occupational categories, age, and gender), the results of the present study are compatible with earlier reports. After controlling for tobacco smoking, women had higher EPPL values and there was a slight negative association of EPPL with age, in line with the findings reported by Auerbach et al.[20] Also, broad occupational categories are not expected to show substantial variability in lung cancer risk, even though particular occupations have definitely been shown to be at increased risk. Furthermore, categorization of occupations is not adequately standardized in Greece, and the lack of association between occupation and lung pathology may be due to inadequate information on occupation.

There were substantially and significantly higher EPPL values among smokers and higher, but not significantly so, EPPL values among past smokers. The lack of dose-response patterns is not surprising. Next of kin responders frequently remember whether the deceased was a smoker, but it is rather unusual for them to have accurate knowledge of the number of cigarettes smoked daily. The resulting nondifferential misclassification is likely to attenuate any existing dose-response pattern to the point of nondetectability in studies of moderate size. It is also possible that heavy smokers with extensive pathological lesions in the lung become symptomatic and thus less likely to be included among those who would be autopsied after their death; a similar selection with respect to passive smokers is implausible, since very few, if any, among them would have such extensive pathological lesions.

The finding concerning passive smoking is statistically significant and adds to the substantial body of evidence linking exposure to environmental tobacco smoke with lung cancer.[3-11] Although the examined subjects represent a selected sample, there is no likely selection factor that could affect the joint distribution of any of the exposure variables and EPPL (over and beyond their actual associations), since all EPPL and RI assessments were done blindly in a different center. Furthermore, selective recollection and other types of biases that have been invoked by some authors[12,13] to explain, in noncausal terms, the association of passive smoking with lung cancer are either nonapplicable or highly unlikely in the context of an autopsy-based study.

The apparent effect of passive smoking may seem too large in comparison to the effect of active smoking in this investigation. Thus, the odds ratio for an EPPL score of 60 or more contrasted to an EPPL score of less than 40 was 0.9 for mainly urban residents (compared with mainly rural residents), 1.4 for former smokers (compared with nonsmokers), and 4.4 for active smokers (compared with nonsmokers), whereas among nonsmoking women the odds ratio was 6.0 for those married to smokers (compared with those married to nonsmokers). The corresponding odds ratios for an RI of 2.5 or higher contrasted to an RI of less than 2.0 were 1.5, 1.7, 2.4, and 1.3. However, EPPL and RI differences and the odds ratios describing the effects of active and passive smoking are not directly comparable. Active smokers are compared with nonsmokers, whether these were exposed or nonexposed to the passive smoking indicator (husband's smoking), whereas passive smokers are compared with subjects unexposed to the passive smoking indicator. It has been pointed out by Vutuc[26] and others[27] that whenever the proportion of nonsmokers who are passive smokers is large (as in the present study or in any setting in which a large majority of men but only a small minority of women are smokers) and the impact of passive smoking is modest or substantial, the effect of active smoking can be grossly underestimated. In the present study, changing the reference group from "nonsmokers" to "nonsmokers unexposed to the passive smoking indicator" would increase the odds ratio for active smoking to almost 10 (with reduced precision, since there would be few subjects in this new reference group). Other factors must also be taken into account. Confidence intervals for passive smokers are fairly large, and they could easily accommodate predicted ratios of effects of active and passive smoking. In addition, the information concerning active smoking of the deceased was obtained from proxy sources, whereas information concerning passive smoking was obtained, in many instances, from individuals who were themselves the sources of this exposure for the deceased. In the former situation nondifferential misclassification is more extensive than in the latter, and the resulting effect

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attenuation is correspondingly larger. Moreover, many smokers, even in Greece, have switched to low tar and nicotine cigarettes, and this should be expected to modify the effects of active smoking[24] while having little, if any, impact on the concentration and composition of environmental tobacco smoke (low tar and nicotine cigarettes are made so by the filter rather than by the composition of tobacco). Last, there is other evidence[27,28] that exposure to environmental tobacco smoke could be more injurious to health than it would be predicted to be on the basis of cotinine excretion studies.

The present data cannot substantiate or challenge the notion that air pollution, of the type and levels present in Athens, is an important determinant of EPPL and, inferentially, lung cancer. Ascertainment of exposure to air pollution on the basis of the residential history, as elicited through a proxy interview, is probably inadequate; furthermore, EPPL is a composite index, some of the components of which may be weak or no predictors of lung cancer risk, thus reducing the overall sensitivity and predictive power of EPPL. Overall, the results of the present investigation do not deviate from the "negative" evidence generated by other pathology-focused studies that have attempted to examine the effect of general air pollution on lung cancer risk,[29] and cannot facilitate the resolution of this important and controversial issue.[29-61]

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References

1. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B. Lung cancer and passive smoking. *Int J Cancer*. 1981;27:1-4.
2. Hirayama T. Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. *BMJ*. 1981;282:183-185.
3. Surgeon General. *The Health Consequences of Involuntary Smoking: A Report*. Rockville, Md: US Dept of Health and Human Services, Public Health Service, Centers for Disease Control, Center for Health Promotion and Education, Office on Smoking and Health; 1985. DHHS (CDC) 87-8398:332.
4. *Tobacco Smoking*. Lyon, France: World Health Organization, International Agency for Research on Cancer; 1986;28. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans.
5. National Research Council, Committee on Passive Smoking. *Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects*. Washington, DC: National Academy Press; 1986.
6. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? *BMJ*. 1986;293:1217-1222.
7. Trichopoulos D. Passive smoking and lung cancer: the Ipsen Lecture 1987. *Scand J Soc Med*. 1988;16:75-79.
8. Saracci R, Riboli E. Passive smoking and lung cancer: current evidence and ongoing studies at the International Agency for Research on Cancer. *Mutat Res*. 1989;222:117-127.
9. Kalandidi A, Katsouyanni K, Voropoulou N, Bastas G, Saracci R, Trichopoulos D. Passive smoking and diet in the etiology of lung cancer among nonsmokers. *Cancer Causes Control*. 1990;1:15-21.
10. Janerich DT, Thompson DW, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. *N Engl J Med*. 1990;323:632-636.
11. Riboli E, Preston-Martin S, Saracci R, et al. Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. *Cancer Causes Control*. 1990;1:243-252.
12. Lee PN. Passive smoking and lung cancer association: a result of bias? *Hum Toxicol*. 1987;6:517-524.
13. Lee PN. Lung cancer and passive smoking: association an artefact due to misclassification of smoking habits? *Toxicol Lett*. 1987;35:157-162.
14. Everingham R, Woodward S, eds. *Tobacco Litigation: AFCO v TIA: The Case Against Passive Smoking*. Sydney, Australia: Legal Books; 1991.
15. Agapitos E, Delsedime L, Kalandidi A, et al. Correlation of early pathological lesions in the bronchial tree with environmental exposures: study objectives and preliminary findings. In: Riboli E, Delendi M, eds. *Autopsy in Epidemiology and Medical Research*. Lyon, France: International Agency for Research on Cancer; 1991:253-268.
16. Auerbach O, Petrick T, Stout A, et al. The anatomical approach to the study of smoking and bronchogenic carcinoma: a preliminary report of forty-one cases. *Cancer*. 1956;9:76-83.
17. Auerbach O, Gere B, Forman J, et al. Changes in the bronchial epithelium in relation to smoking and cancer of the lung. *N Engl J Med*. 1957;256:97-104.
18. Reid L. Measurement of the bronchial mucous gland layer: a diagnostic yardstick in chronic bronchitis. *Thorax*. 1960;15:132-141.
19. Carroll R. Changes in the bronchial epithelium in primary lung cancer. *Br J Cancer*. 1961;15:215-219.
20. Auerbach O, Stout A, Hammond C, Garfinkel L. Changes in bronchial epithelium in relation to sex, age, residence, smoking and pneumonia. *N Engl J Med*. 1962;267:111-119.
21. Auerbach O, Stout A, Hammond C, Garfinkel L. Bronchial epithelium in former smokers. *N Engl J Med*. 1962;267:119-125.
22. Field WE, Davey EN, Reid L, Rose FJ. Bronchial mucus gland hypertrophy: its relation to symptoms and environment. *Br J Dis Chest*. 1966;60:66-80.
23. Cosio M, Ghezzo H, Hogg J, et al. The relations between structural changes in small airways and pulmonary-function tests. *N Engl J Med*. 1977;298:1277-1281.
24. Auerbach O, Hammond C, Garfinkel L. Changes in bronchial epithelium in relation to cigarette smoking, 1955-1960 vs. 1970-1977. *N Engl J Med*. 1979;300:381-386.
25. Cosio M, Hale K, Niewoehner D. Morphologic and morphometric effects of prolonged cigarette smoking on the small airways. *Am Rev Respir Dis*. 1980;122:265-271.
26. Mollo F, Bollati A, Bergia R, Colombo A. Bronchial mucus gland enlargement in 'healthy' subjects: an autopsy survey on 343 cases of traumatic death, in Turin. *Pathologica*. 1981;73:185-192.
27. Wright JL, Lawson LM, Paré PD, Kennedy S, Wiggs B, Hogg JC. The detection of small airways disease. *Am Rev Respir Dis*. 1984;129:989-994.
28. Mullen JB, Wiggs BR, Wright JL, Hogg JC, Paré PD. Nonspecific airway reactivity in cigarette smokers. *Am Rev Respir Dis*. 1986;133:120-125.
29. Whimster WF. Tracheobronchial submucous gland profiles in smokers and non-smokers. *Appl Pathol*. 1988;6:241-246.
30. Vine MF, Schoenbach VJ, Hulka BS, Koch GG, Samsa G. Atypical metaplasia and incidence of bronchogenic carcinoma. *Am J Epidemiol*. 1990;131:781-793.
31. Bosken CH, Wiggs BR, Paré PD, Hogg JC. Small airway dimensions in smokers with obstruction to airflow. *Am Rev Respir Dis*. 1990;142:563-570.
32. Wright JL, Cosio M, Wiggs B, Hogg JC. A morphologic grading scheme for membranous and respiratory bronchioles. *Arch Pathol Lab Med*. 1985;190:163-165.
33. Thurlbeck WM, ed. *Pathology of the Lung*. New York, NY: Thieme Medical Publishers; 1988:523-533.
34. Tannenbaum A, ed. Report of the Working Group on Inhalation Carcinogenesis, with special reference to cigarette smoke. *Int J Cancer*. 1970;5:282-285.
35. Solomon MD, Greenberg DS, Spjut HJ. Morphology of bronchial epithelium adjacent to adenocarcinoma of the lung. *Mod Pathol*. 1990;3:684-687.
36. Vutuc C. Quantitative aspects of passive smoking and lung cancer. *Prev Med*. 1984;13:658-704.
37. Glantz SA, Parmley WW. Passive smoking and heart disease: epidemiology, physiology and biochemistry. *Circulation*. 1991;83:1-12.
38. Wells AJ. Breast cancer, cigarette smoking and passive smoking. *Am J Epidemiol*. 1991;133:208-210.
39. Henderson DB, Gordon RJ, Menck H, Soohoo J, Martin SP, Pike MC. Lung cancer and air pollution in southcentral Los Angeles County. *Am J Epidemiol*. 1975;101:477-488.
40. Blot WJ, Fraumeni JF. Geographic patterns of lung cancer: industrial correlations. *Am J Epidemiol*. 1976;103:539-550.
41. Canvow BW. The 'urban factor' and lung cancer: cigarette smoking or air pollution? *Environ Health Perspect*. 1978;22:17-21.
42. Ford AB, Bialic O. Air pollution and urban factors in relation to cancer mortality. *Arch Environ Health*. 1980;25:250-359.
43. Hammond EC, Garfinkel L. General air pollution and cancer in the United States. *Prev Med*. 1980;9:206-211.
44. Matanoski GM, Landau E, Tonascia J, et al. Cancer mortality in an industrial area of Baltimore. *Environ Res*. 1981;25:8-28.
45. Weinberg GB, Kuller LH, Redmond CK. The relationship between the geographic distribution of lung cancer incidence and cigarette smoking in Allegheny County, Pennsylvania. *Am J Epidemiol*. 1982;115:40-58.
46. Vena JE. Air pollution as a risk factor in lung cancer. *Am J Epidemiol*. 1982;116:42-56.
47. National Research Council, Committee on the Epidemiology of Air Pollutants, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences. *Epidemiology and Air Pollution*. Washington, DC: National Research Council, National Academy Press; 1985.
48. Butler PA, Cooper SP, Stinnett S, et al. Air pollution and lung cancer mortality in Harris County, Texas, 1979-1981. *Am J Epidemiol*. 1988;128:683-699.
49. Zu Z-Y, Blot WJ, Xiao H-P, et al. Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. *J Natl Cancer Inst*. 1989;81:1800-1806.
50. Pershagen G, Simonato L. Epidemiological evidence on air pollution and cancer. In: Tomatis L, ed. *Air Pollution and Human Cancer*. New York, NY: Springer-Verlag NY Inc; 1990:53-74. European School of Oncology Monograph.
51. Katsouyanni E, Trichopoulos D, Kalandidi A, Tomos P, Riboli E. A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. *Prev Med*. 1991;20:271-278.

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